GUIDANCE[1]

CIMETIDINE TABLETS

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION

I. INTRODUCTION

A. Clinical Usage

Cimetidine is a histamine H_2-receptor antagonist, used for the treatment of endoscopically or radiographically confirmed duodenal ulcer, pathologic GI hypersecretory conditions (e.g., Zollinger-Ellison syndrome, systemic mastocytosis, and multiple endocrine adenomas), and active, benign, gastric ulcer.

Cimetidine inhibits competitively and selectively the interaction of histamine with H_2 receptors. It inhibits basal (fasting) and nocturnal acid secretion and that stimulated by food, sham feeding, fundic distention, and various pharmacological agents.

Effective cimetidine concentrations between 0.5 and 1.0 µg/ml are required to suppress gastric acid secretion under basal or stimulated conditions. However, no correlation between plasma concentrations of cimetidine, or any of the pharmacodynamic parameters

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[1]This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-295-8290; Fax: 301-295-8183).

and duodenal ulcer healing rate has been established to predict successfully therapeutic response from pharmacokinetic data.

Adverse effects of cimetidine include diarrhea, dizziness, somnolence, reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), gynecomastia, reversible impotence, decrease in white blood cell counts, increase in serum transaminase and mild rash.

Cimetidine is available commercially as Tagamet^{R} (Smith-Kline Beecham) oral, film-coated tablets, in 200, 300, 400 and 800 mg strengths. For treatment of active duodenal ulcer, the usual adult oral dosage of cimetidine is 800 mg daily at bedtime. For maintenance therapy following healing of acute duodenal ulcer, the usual oral dosage of cimetidine is 400 mg daily at bedtime. For the treatment of pathologic hypersecretory conditions, the usual adult oral dosage is 300 mg, 4 times daily with meals and at bedtime. For the treatment of active benign gastric ulcer, the usual adult oral dosage is 800 mg at bedtime or 300 mg, 4 times daily with meals, and at bedtime.

B. Chemistry

Cimetidine contains an imidazole ring and is structurally similar to histamine. Unlike the histamine H2-receptor antagonists burimamide and metiamide, which are not commercially available, cimetidine contains a cyanoguanidine group rather than a thiourea moiety. Cimetidine is a weak base and highly water-soluble compound. Cimetidine has a pK_a of 6.8, and cimetidine hydrochloride has a pK_a of 7.11. The chemical structure of cimetidine appears in the following figure:

C. Pharmacokinetics

Following intravenous administration, the plasma concentration profile follows multicompartmental characteristics. The total systemic clearance is high (500 to 600 ml/min) and is mainly determined by renal clearance. The volume of distribution is of the order of 1 L/kg. Elimination half-life is approximately 2 hours. Following oral administration of cimetidine, 2 plasma concentration peaks are frequently observed at about 1 hour and after about 3 hours, probably due to discontinuous absorption in the intestine or individual variation in gastric emptying (but not enterohepatic recycling since the biliary excretion rate in man is less than 2%). The absolute bioavailability is about 60% in healthy subjects and around 70% in peptic ulcer patients. Absorption and clearance of cimetidine are linear after 200 and 800 mg doses. When given with food, the extent of absorption of the drug remains unchanged but the time to reach the maximum peak concentration is delayed with only one peak in the plasma concentration curve observed at about 2 hours. Plasma protein binding of cimetidine is 20% and does not significantly affect the pharmacokinetics of the drug. Cimetidine distributes extensively into kidney, lung and muscle tissues, but less than 1% into the cerebrospinal fluid.

Following IV administration, about 50 to 80% of the dose is recovered in urine as unchanged cimetidine. This fraction is less after oral doses. Biliary excretion of cimetidine accounts for about 2%. About 25-40% of the cimetidine dose is eliminated as metabolites, formed mainly in the liver. The metabolites are sulphoxide and 5-hydroxymethyl derivatives, and possibly guanylurea, although this latter compound may result from *in vitro* degradation. Elimination of cimetidine is accelerated in the presence of phenobarbital due to induction of its metabolism. Clearance of the drug is higher in children, who have greater renal elimination mechanisms. With increased age, the volume of distribution of the drug decreases, total plasma clearance decreases as a function of decreasing renal clearance, and plasma half-life increases.

II. *IN VIVO* BIOEQUIVALENCE STUDIES

A. Types of Studies Required

1. A single-dose, fasting, two-way crossover study with the 800 mg strength generic Cimetidine test product compared to the reference product Tagamet® 800 mg tablet.

2. A single-dose, two-way crossover, full food study with the 800 mg strength of the generic Cimetidine test product compared to the reference product Tagamet® 800 mg tablet. **Due to the double-peak phenomenon which is only observed under fasting conditions, the food study may be more reliable for determining the bioequivalency of the test product and therefore should be done with a full complement of subjects.**

B. Fasting Study

Objective: The objective of this study is to compare the bioavailability of a generic Cimetidine 800 mg tablet (test product) with the reference product Tagamet® 800 mg tablet under fasting conditions.

Design: The study design is a single dose, two treatment, two period, two sequence crossover with a washout period of at least 7 days. Subjects should be randomly assigned to the two possible dosing sequences.

Facilities: The clinical and analytical sites for the study should be given along with the names, titles and the curriculum vitae of the medical, scientific and analytical directors. The starting and ending dates for each clinical study period should be stated. The study protocols should be approved by an institutional review board, and informed consent forms should be signed by all participants.

Subjects: A minimum of 24 normal, healthy male subjects should be used. The study subjects should be approximately 19-45 years of age, and within 10% of the ideal weight for their height and body frame according to the Metropolitan Insurance Company Bulletin, 1983. All subjects should be given a physical examination and appropriate laboratory tests 4 weeks prior to the initiation of the study. These should be repeated at

the end of the study. They should have no history of cardiovascular, hematologic, gastrointestinal, hepatic, renal, pulmonary, neurologic or psychiatric disease, substance abuse, or hypersensitivity to cimetidine or any H_2-receptor antagonist.

Restrictions: Subjects should be free of all medications at least two weeks prior to the start of the study, with no concomitant medications allowed during the study. They should consume no alcohol, caffeine or xanthine-containing products for 48 hours prior to and during each study session. They should fast for at least 10 hours prior to and 4 hours following each drug administration.

Procedures: After an overnight (at least 10 hours) fast, subjects should receive a single dose of the test product or the reference product with 240 ml of water:

Treatment A: Test product, 1 x 800 mg cimetidine tablet

Treatment B: Reference product, 1 x 800 mg Tagamet® (Smith-Kline Beecham) tablet

The test product should be from a production lot or from a lot produced under production conditions. The lot size of the test product should be equal to or more than 100,000. The lot numbers of both the test and reference products and the expiration date for the reference product should be stated. The potency of the reference product should not differ from that of the test product by more than $\pm$ 5%. The sponsor should include a statement of the composition of the test product.

Blood Sampling: Blood samples should be collected at predose, 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20 and 24 hours following drug administration.

Analytical Methodology: The plasma levels of cimetidine should be determined using a validated analytical assay. The assay specificity, linearity, reproducibility, sensitivity and accuracy should be demonstrated fully. Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be

determined. Plasma quality controls of low, medium and high concentrations of cimetidine should be included in every run to establish, along with the standard curve, the acceptability of a run, and to determine the intraday and interday variations in the analytical method. The firm should have clear, unbiased Standard Operating Procedures on acceptance criteria for standard values and quality control values, reasons for repeating a sample and a basis for reporting a final value of samples that are repeated. As shown in recent literature, there are available several simple, sensitive and specific HPLC analytical assays for cimetidine (see references).

Pharmacokinetic Analysis: The plasma concentration of cimetidine of each subject at every sampling point should be reported for all subjects. The following pharmacokinetic parameters should also be obtained by the sponsor:

1. AUC_{0-t}, calculated by the trapezoidal rule, where t is the last measurable time point.

2. $AUC_{0-\infty}$, where $AUC_{0-\infty} = AUC_t + C_t/(\lambda_Z)$, C_t is the last measurable drug concentration and λ_Z is the terminal elimination rate constant.

3. The terminal phase elimination rate constant (λ_Z) is calculated using an appropriate pharmacokinetic method.

4. Peak drug concentration (C_{max}), first peak concentration ($C_{max\ first\ peak}$) if there are two peaks, and the time to peak drug concentration (T_{max} or $T_{max\ first\ peak}$) are obtained directly from the data without interpolation.

Statistical Analysis: The sponsor should perform the following tests:

1. Analysis of variance (ANOVA) appropriate for a crossover design on the pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} using General Linear Models (GLM) procedure of SAS or an equivalent program should be performed. The statistical model should include terms describing the effects attributable to sequence, subject(sequence), period, and

treatment. The sequence effect should be tested using the between-subject main effect [subj(seq)] as an error term. All other main effects should be tested against the residual error (error mean square) from the ANOVA.

2. The ESTIMATE statement in SAS should be used to obtain estimates for the adjusted differences between treatment means and the error associated with these differences.

3. The LSMEANS statement should be used to calculate least-square means for treatments.

4. The two one-sided tests procedure should be used to calculate 90% confidence intervals for the mean difference for AUC, C_{max}, and $C_{max\ first\ peak}$ which should generally be within $\pm$ 20% of the corresponding reference mean.

Adverse Reactions: The sponsor should report all adverse reactions that occurred during the study with regard to the nature, onset, duration, frequency, severity, type of treatment during which the reaction occurred and the suspected relation to the drug treatment.

C. Two-Way Postprandial Study

There should be at least 24 healthy male volunteers. The postprandial study should be conducted in the same manner as described for the fasting study except under fed conditions. The subjects should be given a standard high-fat breakfast (consisting of one buttered English Muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hash brown potatoes, 6 fluid ounces (180 ml) of orange juice and 8 ounces of whole milk) after an overnight fast of approximately 10 hours. The dose should be given with 240 ml of water approximately 30 minutes after beginning breakfast. The plasma cimetidine data should be obtained and analyzed in the same manner as described for the fasting study. Due to the double-peak phenomenon which is only observed under fasting conditions, the postprandial study may be more reliable for determining the bioequivalency of a test product.

III. *IN VITRO* TESTING

A. Dissolution Testing

Dissolution testing should be conducted on 12 dosage units of the test product versus 12 units of the reference product. The same lots used in the *in vivo* bioequivalence study should be tested. The following procedure should be used:

Apparatus:	USP XXII apparatus 1(basket)
RPM:	100
Medium:	Deaerated water
Volume:	900 ml
Sampling Times:	10, 15 and 30 minutes
Tolerance:	NLT 75% in 15 minutes

The sponsor should include the following information from dissolution testing:

1. Lot numbers for both test and reference products.

2. The percent dissolution for each dosage unit being tested at each time interval.

3. The mean percent dissolved, the range of percent dissolution and the coefficient of variation for the 12 units being tested at each time interval.

4. Validation data for the analytical method used.

5. Expiration date for the reference product.

B. Content Uniformity Test

Content uniformity of 10 test product dosage units from the lot used in the dissolution testing should be determined and the data should be submitted along with the dissolution data.

C. Potency

Prior to initiation of the *in vivo* bioequivalence study, the applicant should determine the potency of the lot of the test drug product to be used in the study. It is recommended that the applicant should ensure that the potency of the lot of the test product to be used in the bioequivalence study is within ± 5%

of that of the reference product. The data on potency should be submitted along with the bioequivalence results.

IV. WAIVER REQUEST

For the 400 mg, 300 mg and 200 mg tablets of cimetidine, the bioequivalence requirement will be deemed to have been met under the following conditions:

1. The 400 mg, 300 mg and 200 mg tablets are proportionally similar in their active and inactive ingredients to the 800 mg tablet which underwent a bioequivalence study; and

2. The 400 mg, 300 mg and 200 mg tablets display satisfactory dissolution characteristics compared to the same strengths of the reference product, Tagamet® tablets.

V. REFERENCES

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